NCT# 01596751

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Study Title: CC#12751: Enhancing Efficacy of Chemotherapy in Triple Negative/Basal-Like Breast Cancer by Targeting Macrophages: A Multicenter Phase Ib/II study of PLX 3397 and Eribulin in Patients with Metastatic Breast Cancer

This is a clinical trial, a type of research study. Your study doctor, Dr. Hope Rugo, and her associates from the UCSF Department of Medicine, will explain the clinical trial to you.

Clinical trials include only people who choose to take part. Please take your time to make your decision about participating. You may discuss your decision with your family and friends and with your health care team. If you have any questions, you may ask your study doctor.

You are being asked to take part in this study because you have breast cancer that has spread to other parts of your body (metastatic breast cancer) and you have had at least one prior chemotherapy treatment for the advanced disease.

WHY IS THIS STUDY BEING DONE?

The purpose of the Phase 1b portion of the study is to determine the best dose of PLX3397 when given in combination with standard dose eribulin (Halaven™). The purpose of the Phase 2 portion of the study is to find out what effects, good and/or bad, these drugs have on you and your cancer.

PLX3397 is a new drug that blocks certain receptors, or targets, on cancer cells. This activity will be used to attack tumors in a number of different ways: by directly preventing cancer related cells from turning on, by stopping cancer cells from communicating with each other, and by blocking cancer cells from migrating to other parts of your body and the blood supply cancer cells need for growth.

PLX3397 is an investigational drug, which means it has not been approved for use by the US Food and Drug Administration (FDA). Eribulin is a drug that has been approved by the FDA for metastatic breast cancer. However, the combination of eribulin and PLX3397 is considered experimental; that means this combination has not been approved by the FDA.

The Susan G. Komen foundation is providing funding to UCSF to conduct the study. Plexxikon Inc., the manufacturers of PLX3397, will provide PLX3397 at no cost to study participants.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

Up to 24 patients will participate in this study in the first portion of this study (Phase 1b) at UCSF, Vanderbilt University, and Duke University. About 10 patients will be enrolled at UCSF.

Up to 61 patients will participate in the phase 2 portion at UCSF, Vanderbilt University, and Duke University. About 26 patients will be enrolled at UCSF. A total of 85 patients will be enrolled for both phases at all sites.

WHAT WILL HAPPEN IF I TAKE PART IN THIS RESEARCH STUDY?

This study is a two part study. Your study doctor will tell you which part and dose group you will be participating in prior to your enrollment.

Phase 1b will determine the highest dose level (maximum tolerated dose) of PLX3397 to give in combination with eribulin. The best dose tolerated by patients in Part 1 will be used as the dose level in Part 2 of this study. The Phase 1b portion of this study is now closed to accrual.

Phase 2 will look at how the maximum tolerated dose of PLX3397 in combination with eribulin affects your cancer and your body.

Study Drug

PLX3397 is given in capsule form. In this research study, each "cycle" of treatment usually lasts 21 days. You will be given a supply of PLX3397 on Day 1 of each cycle to last a whole cycle. You will take PLX3397 by mouth 5 days on, 2 days off. You should fast (not eat anything) for at least 1 hour before taking your PLX3397 and 1 hour after taking your PLX3397. You may eat a low-fat, bland snack (e.g., crackers, toast, tea) during the fasting period if needed (for example, if you are feeling nauseous or weak).

You will be provided with a drug diary where you will record each date you take the study drug. If you forget to take your scheduled dose, you should not make up the missed dose. Any missed doses should be recorded on the dosing diary. You will be required to bring your dosing diary with you to every visit.

The doses of PLX3397 will be increased throughout the trial in Phase 1b. Patients participating in Phase 1b will be assigned to one specific dose level and will continue receiving that same dose while on treatment. However, if you have side effects that seem to be due to the drug, your study doctor may decrease your dose or take you off of study drug. The dose escalation portion of the study will end when it has been determined what dose of the study drugs are determined to be the safest for study participants. This is also called the maximum tolerated dose or MTD. Patients in Phase 2 will receive the MTD of PLX3397.

Eribulin is given intravenously (IV). You will receive eribulin on days 1 and 8 of each cycle during your study visit. You may be given medications that are chosen by your study doctor prior to the eribulin infusion to help with allergic reactions. If you are given these pre-eribulin medications, please ask your study doctor about any risks associated with those medications.

(Note: standard dosing of eribulin is Day 1 and Day 8 every 21 days. For this study, if you started on a modified dosing of eribulin (Day 1 and 15 every 28 days), you will remain on the modified dosing schedule. The modified dosing was implemented to make the combination of

eribulin and PLX3397 more tolerable and to reduce bone marrow suppression from eribulin. All other patients will start on the standard dosing schedule. Your study doctor will let you know which schedule you will be on.)

Before you begin the study...
If you choose to participate in this study you will have several screening tests to see if you can take part. Most of these are procedures that you would have as part of your regular cancer treatment even if you did not participate in this study. You will also have some procedures that are only being done because you are in the study. These are called research procedures and are noted as "research purposes" in the list of procedures below. If you have had some of these procedures recently, they may not need to be repeated. This will be up to your study doctor.

You must complete your Screening procedures within 14 days prior to receiving the study drug. Your screening visit may take up to 6 hours depending on which procedures you have.

- Medical history - You will be asked about your health, any current and past illnesses, and medications you are taking and those you have taken
- Physical exam, including measurements of vital signs, height, and weight
- Questions about how your disease is affecting your daily life
- Electrocardiogram (ECG) - An ECG records the electrical activity of your heart. Wires or "leads" will be attached to your chest with an adhesive and you will be asked to lie still while the machine prints out an electrical "record" of your heart activity. This takes about 15-30 minutes – research purposes
- Blood (about 2 tablespoons) will be drawn:
  - For routine laboratory tests
  - To classify different white blood cells in your blood
- Pregnancy test - if you are a woman of childbearing age
- Tumor assessment by CT (Computed Tomography) scan, PET CT (Positron Emission Tomography) scan, or Bone Scan. Patients with bone-only disease will have a CT scan and bone scan or PET CT scan. Your doctor will let you know which scan you will need to have.
  - A CT scan uses special x-ray equipment to make detailed pictures of body tissues and organs. For the CT scan, you may be given a "contrast material" (a special dye that makes it easier for doctors to see different tissues in your body). The contrast material may be given orally, intravenously, or rectally (less likely). Oral contrast material is given to you to drink and is used to help outline the stomach and intestines. Intravenous (IV) contrast material is given to you by injecting the contrast material into a line which is attached to a needle in your arm, and is used to get clearer pictures of your body cavity. A rectal contrast fills up the loops of your lower bowel so the doctors can see your tumor better. After you have been given the contrast material (either by mouth, by vein, or rectum), you will lie flat on a table that will move you into the CT scan machine. You will be asked to lie still and may be asked to hold your breath for a few seconds. The CT scan is done in the radiology department and takes about half an hour.
  - For the PET CT, an IV is started in the hand. A small amount of radioactive chemical (glucose) is injected into the blood stream. Once the glucose is injected, you will be asked to wait for about an hour to allow for glucose to distribute in the body. Then you

will be asked to lie down on a table and the body is scanned. The total time one will spend at the clinic is about 2-3 hours.
  - A bone scan is a test that makes detailed images of your bones and any tumors on them. Before the bone scan a small amount of radioactive substance is injected into your vein. About 3 hours later you will lie on a table under a machine which will make an image of your bones. The test itself will take about 1 hour, but the whole process takes up to 4 hours.
- Tumor tissue collection - Your tumor sample (either fresh biopsy tissue collected during the study or leftover tissue from a previous biopsy or surgery) will be used to identify biomarkers (specific traits) of your cancer that may predict a person's response to this type of treatment or possibly response to PLX3397 treatment – research purposes.
  - Biopsy for patients with accessible tumor - A biopsy procedure will involve removing all or part of your tumor. Usually, this biopsy involves the use of a small needle which is directed into your tumor site with the guidance of an imaging machine such as a CT scan or a Doppler ultrasound, if necessary. A tumor biopsy will take 30-60 minutes depending on the location of the biopsy.
  - Leftover tumor tissue collection – If available, the researchers would like to get a sample of leftover tumor tissue from any biopsy or surgery you may have had as part of your regular cancer care. Any remaining tumor tissue not used for the biomarker study will be returned to the clinic/hospital from which they were obtained.

During the main part of the study...
If the screening exams, tests and procedures show that you can be in the main part of the study, and you choose to take part, you will have the following procedures. Patients participating in Phase 1b and Phase 2 will have the same procedures listed below performed unless otherwise noted. A schedule of assessments for Phase 1b and Phase 2 has been included at the end of the consent form. Your clinic visits may take about 1 hour. If your visit includes blood studies to determine the levels of study drug in your blood or tumor assessments, your clinic visit may take up to 5-6 hours.

Cycle 1, Day -7/-6 (6 to 7 days before starting eribulin treatment) - *Phase 2 only*
- Questions about how your disease is affecting your daily life
- Blood (about 1 tablespoon) will be drawn:
  - To classify different white blood cells in your blood – research purposes
  - To monitor CSF1 (proteins produced by cells in your body) levels – research purposes
- You will start taking PLX3397

Cycle 1, Day 0/-2 (0 to 2 days before starting eribulin treatment) – *Phase 2 only*
- Tumor Biopsy

Cycle 1, Day 1
- *Do not eat for one hour prior to your appointment.* You may be allowed to have a bland, low-fat snack (crackers, toast, tea, etc.) if needed during this 1-hour period – ***Phase 1 only***

- Medical history - You will be asked about your health, any current and past illnesses, and medications you are taking and those you have taken
- Physical exam, including measurements of vital signs, height, and weight
- Questions about how your disease is affecting your daily life
- Blood (about 4-5 tablespoons) will be drawn:
  - For routine laboratory tests
  - To monitor CSF1 (proteins produced by cells in your body) levels – research purposes
  - For pharmacokinetic (PK) studies – The studies will determine the levels of study drug in your blood at different time points. Blood will be drawn before your drug dosing and at one, two and 5 hours post dosing – research purposes. ***Phase 1 only***
  - To classify different white blood cells in your blood – research purposes.
- You will receive eribulin (IV)

Cycle 1, Day 2 - *Phase 1 only*

- *Do not take your morning dose of PLX3397 until you are instructed to do during your clinic visit.*
- Blood (about 1 tablespoon) will be drawn:
  - For PK – blood will be drawn at 24 hours post Day 1dosing – research purposes

  To monitor CSF1 (proteins produced by cells in your body) levels – research purposes

Cycle 1, Day 8

- Medical history - You will be asked about your health, any current and past illnesses, and medications you are taking and those you have taken
- If you are having any symptoms, you will have a Physical exam to check those symptoms
- Questions about how your disease is affecting your daily life
- Blood (about 1 tablespoon) will be drawn:
  - For routine laboratory tests
- You will receive eribulin (IV)

***Patients on the modified eribulin dosing schedule will have this visit performed on Day 15.*

Cycle 1, Day 15

- Blood (about 1 tablespoon) will be drawn:
  - For liver function tests

Cycle 2 and beyond, Day 1

- *Do not take your morning dose of PLX3397 until you are instructed to do so during your clinic visit. Do not eat for one hour prior to your appointment.* You may be allowed to have a bland, low-fat snack (crackers, toast, tea, etc.) if needed during this 1-hour period – ***Cycle 2, Phase 1 only***
- Medical history - You will be asked about your health, any current and past illnesses, and medications you are taking and those you have taken
- Physical exam, including measurements of vital signs, height, and weight

- Questions about how your disease is affecting your daily life
- Blood (about 5 tablespoons) will be drawn for:
  - Routine laboratory tests
  - The following blood samples will only be drawn in Cycle 2 and Cycle 4 -
    - To monitor CSF1 (proteins produced by cells in your body) levels – research purposes
    - To classify different white blood cells in your blood – research purposes
    - For PK studies - blood will be drawn before your drug dosing and two hours post dosing – research purposes ***Phase 1 only***
- ECG – ***Cycle 2, Phase 1 & Phase 2***
- You will receive eribulin (IV)

Cycle 2 and beyond, Day 8

- Blood (about 1 tablespoon) will be drawn for routine laboratory tests
- You will receive eribulin (IV)

***Patients on the modified eribulin dosing schedule will have this visit performed on Day 15.*

Cycles 2 and 3, Day 15

- Blood (about 1 tablespoon) will be drawn:
  - For liver function tests

Every 6 or 8 weeks (Your study doctor will inform you which schedule you will be on.)

- Tumor assessment by CT scan, PET CT scan, or Bone Scan
- ECG – ***Phase 1 & Phase 2***

When you are finished receiving PLX 3397 and eribulin...

You will be asked to return to the clinic 30 days after your last dose of study medication for the following additional tests and procedures:

- Medical history - You will be asked about your health, any current and past illnesses, and medications you are taking and those you have taken
- Physical exam, including measurements of vital signs, height, and weight
- Questions about how your disease is affecting your daily life
- Blood (about 1 tablespoon) will be drawn for routine laboratory tests
- Tumor assessment by CT scan, PET CT scan, or Bone Scan

If you experienced any side effects that have not been resolved, you physician may continue to monitor you until these symptoms are resolved or considered stable.

Study Location: UCSF Helen Diller Family Comprehensive Cancer Center.

HOW LONG WILL I BE IN THE STUDY?

You will continue to receive PLX3397 and eribulin as long as your disease does not progress or you do not have severe side effects, you experience any bad side effects, you decide to withdraw your consent to participate in this study, or the study is closed. After you are finished taking the treatment, the study doctor will ask you to visit the office for follow-up exams within 30 days.

CAN I STOP BEING IN THE STUDY?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop your participation safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from PLX3397 and eribulin can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest, if you do not follow the study rules, or if the study is stopped.

WHAT SIDE EFFECTS OR RISKS CAN I EXPECT FROM BEING IN THE STUDY?

There are risks and discomforts that you may experience associated with the research study. These deserve careful thought. You should talk to the study doctor if you have any questions. By taking PLX3397, you may experience one or more of the side effects listed below. The side effects of taking the study treatments may range from mild to severe. The side effects may be severe enough to be life-threatening or fatal.

If you experience severe side effects, your treatment with study drug may be reduced, temporarily discontinued, or permanently discontinued. You will receive appropriate medications and treatment for any side effects as determined to be best for your health by the study doctor.

Side effects that may be seen with PLX3397 given by itself or in combination with other anti-cancer treatments:

Common side effects (≥10% by frequency) associated with the use of PLX3397 include the following:

- Nausea
- Vomiting
- Diarrhea
- Abnormal or altered sense of taste
- Decreased or loss of appetite
- Rash
- Hair or skin color changes, (to white or gray; original color usually returns after stopping study drug)

- Increases in blood tests that monitor for and indicate liver damage (aspartate aminotransferase and/or alanine aminotransferase)
- Anemia (decrease in red blood cells that may make you weak or tired)
- Fatigue or tiredness

Less common side effects (3% to less than 10%) associated with the use of PLX3397 include the following:

- Constipation
- Increase in bilirubin (produced when the liver breaks down red blood cells)
- Decrease in white blood cell counts (which could include one or more of the following: white blood cell counts, lymphocytes, neutrophils, leukocytes; this may lead to increased risk of infection)
- Febrile neutropenia (fever in a patient with neutropenia, an abnormally low number of neutrophils, a type of white blood cell)
- Decrease in platelets (cells that help stop bleeding)
- Edema (swelling of tissues in limbs, face, or around the eyes)

Additional side effects observed in clinical trials which are less common (3% to less than 10%) and for which association with PLX3397 use is under investigation:

- Dry mouth
- Upset stomach
- Stomatitis (inflammation inside of mouth, usually a small sore or ulcer)
- Fever and/or chills
- Mucosal inflammation (inflammation affecting moist tissue lining parts of the inside of your body, such as mouth, nose, lungs, and digestive tract)
- Pruritus (itching of skin)
- Alopecia (loss of hair)
- Dry skin
- Low levels of electrolytes in blood (which could include one or more of the following: potassium, phosphorus, or sodium)
- Dehydration
- Increase in blood enzyme (which could include one or more of the following: creatine phosphokinase, blood alkaline phosphatase)
- Weight decreased
- Headache
- Dizziness
- Hypertension (high blood pressure)
- Cough
- Dyspnea (difficulty breathing)
- Arthralgia (joint pain)
- Insomnia
- Change in mental abilities such as memory loss and impaired thinking (2%)

PLX3397 may cause liver injury that in some cases can be severe. In a study where PLX3397 was administered on its own and in studies where PLX3397 has been given in combination with other treatments, a form of liver injury called cholestasis has been seen. This is a type of liver injury where the flow of bile from the liver has been impaired causing jaundice (yellowing of the skin) and symptoms of liver disease including itching. Your liver function tests will be followed weekly for the first 9 weeks on study, and then each time you receive chemotherapy. Taking PLX3397 together with other medications may further increase the risk of severe liver injury. The liver injury may persist for a prolonged period (potentially many months), despite discontinuation of study medication, and there is the potential that the liver damage may be permanent or result in liver failure. You may be required to have additional monitoring and evaluation, which may include a liver biopsy. If you develop jaundice, yellowing of the eyes, a change in stool color (to a light color), abdominal pain, itching, or persistent nausea and vomiting you should inform your study doctor immediately.

There has been one report of a patient developing a potentially life-threatening rash after taking PLX3397 and PLX3397 was identified as a potential cause. This type of rash may sometimes include fever and inflammation of internal organs.

Side effects in healthy normal volunteers who received single doses of PLX3397 were all mild or moderate, and mostly associated with the digestive system, including constipation and abdominal bloating/discomfort.

Animals treated with PLX3397 showed decrease in the pumping action (contraction) of the heart. There have been two reports of reduced ejection fraction (the amount of blood pumped by your heart with each beat) in patients receiving PLX3397 at a dose of 3000 mg/day, a much higher dose than you will receive. The role of PLX3397 in these events is undetermined at this time.

The severity of the side effects listed above could range from mild to severe or even life-threatening. In addition, there may be other risks or side effects from PLX3397 that are not listed above or unknown at this time. It is also possible to experience a serious allergic reaction, which could become life-threatening or fatal. Symptoms of an allergic reaction include rash, hives, itching, swelling of the mouth, face, lips or tongue, dizziness, tightness in the chest, or trouble breathing.

If you do not understand what any of these side effects mean, please ask the study doctor or study staff to explain these terms to you.

Your condition may not improve and could even worsen if you take part in this study.

When taking any new medication, you should exercise caution and not drive, operate machinery, or engage in other activities requiring mental alertness until you know how the medication will affect you.

The study drug must be taken only by the person for whom it has been provided. It also must be kept out of the reach of children or persons of limited capacity to read or understand.

Risks and side effects related to the study drug eribulin:

Likely

- Decreased white blood cells (may increase chance of infection)
- Decreased red blood cells (may cause weakness and tiredness)
- Fatigue
- Hair loss
- Peripheral neuropathy (a form of damage to the nerves supplying the hands and feet, which leads to numbness or the feeling of "pins and needles" and/or impairment of muscle strength in the hands and feet)
- Nausea
- Constipation

Less Likely

- Eyes watering
- Upset Stomach/abdominal pain
- Inflammation or ulcers in the mouth (stomatitis)
- Dry mouth
- Fluid retention
- Upper respiratory tract infection
- Low potassium in the blood (can cause constipation, weakness, and abnormal heart rhythms)
- Muscle spasms, muscular weakness
- Change in taste
- Dizziness
- Insomnia
- Depression
- Rash
- Liver function test changes

OTHER RISKS

Study Drug Combination risks: The side effects of the combination of PLX3397 and eribulin are not yet known. It is possible that this combination of drugs will cause new or more serious side effects than taking these drugs separately. You will be monitored closely for side effects and your doctor may change your medications if it appears that this combination is causing serious side effects. You should tell your doctor about any side effects that you experience while on this study. When additional information about side effects is known, you will be notified of any further study drug related effects.

Dose Escalation risks: Only for patients participating in Phase 1b, since patients will be assigned to different doses of study drug, some patients may receive a dose of the drug that is too

small to be effective while others may receive a higher dose that may cause increased side effects. You can ask your study doctor what dose you will be given.

Blood drawing (venipuncture) risks: Drawing blood may cause temporary discomfort from the needle stick, bruising, and infection.

Electrocardiogram (EKG/ECG) risks: The ECG involves placing electrodes on the skin. You may experience an allergic reaction to the adhesive used to attach the electrodes to the skin. These symptoms are generally mild and clear up on their own. Please let your doctor know if you are aware of any allergies.

Radiation (x-ray) risks: The amount of radiation you will be exposed to is relatively small. Such doses of radiation may be potentially harmful, but the risks are so small that they are difficult to measure. If you have already had many x-rays, you should discuss this with the researchers before agreeing to be in the study.

CT Scan risks: CT scans involve the risks of radiation. In addition, if contrast material (iodine dye) is used, there is a slight risk of developing an allergic reaction, from mild (itching, rash) to severe (difficulty breathing, shock, or rarely, death). The contrast material may also cause kidney problems, especially if you are dehydrated or have poor kidney function. The study doctors will ask you about any allergies or related conditions before the procedure. If you have any of these problems, you may not be allowed to have a CT scan with contrast. If you are taking metformin (or similar drugs by mouth to treat high blood sugar), such treatment will be stopped for 2-3 days around the time a scan is planned in order to avoid kidney side effects.

Having a CT scan may mean some added discomfort for you. In particular, you may be bothered by feelings of claustrophobia when placed inside the CT scanner, or by lying in one position for a long time. If contrast material is used, you may feel discomfort when it is injected by vein. You may feel warm and flushed and get a metallic taste in your mouth. Rarely, the contrast material may cause nausea, vomiting or a headache.

PET/CT Scan risks: The PET/CT scan exposes your body to radiation, see radiation risk above. The radiation levels come from a tracer which is a radioactive chemical injected into a vein in your arm. The tracer lets the doctor see how your cells are functioning and the radiation levels are very low. You may have an allergic reaction to the chemical used in the scan. For some patients, having to lie still on the scanning table for the length of the procedure may cause some discomfort or pain. After the scan your arm may be a little bit sore or have some redness where the IV was placed in your arm. The radioactive solution does not remain in your system for a long period of time. However, you should wait 2 hours before holding an infant or getting close to a pregnant woman to avoid exposing them to radiation. You should drink fluids after the scan to help remove the solution from your system.

Bone Scan risks: Risks include radiation exposure as well as possible bruising from the injection of contrast. Some subjects may be uncomfortable lying flat.

Tumor Biopsy risks: The general risks associated with this procedure are pain, discomfort, infection, bleeding and injury to organs nearby.

Reproductive risks: If you become pregnant or father a child while in this research study or 90 days following study completion, you must notify the study doctor immediately. The risk of taking this product in pregnant women has not been fully determined from either human studies or animal studies. There is no clinical experience in humans with PLX3397 in pregnant or lactating women. PLX3397 can cause fetal defects in rodents and rabbits, and should be considered potentially harmful to the fetus, with the potential to cause fetal malformations. As a result, PLX3397V should not be administered to pregnant women or lactating women who arebreastfeeding. You should avoid becoming pregnant over the course of this study. Becoming pregnant while participating in the study will expose you to a potential loss of the pregnancy, or other unknown effects on an unborn child, such as but not limited to, birth defects and premature delivery. You will be withdrawn from the study if you become pregnant or have a positive pregnancy test. In animal studies, PLX3397 caused a decrease in sperm count and changes in the

ovaries which were reversible at the end of the study. PLX3397 may therefore affect fertility in both men and women. If you are a male, you may ask your study doctor about sperm banking.

Unknown Risks: The experimental treatments may have side effects that no one knows about yet. The researchers will let you know if they learn anything that might make you change your mind about participating in the study.

Safe Handling of Chemotherapy Medications

The study drug PLX3397 is labeled as a hazardous medication. Handling PLX3397 and having contact with any urine, feces or vomit from patients receiving PLX3397 may pose some risk to you and your caregivers. To avoid exposure to PLX3397 and any associated risks, you will be educated by a member of the study team on how to safely handle PLX3397, properly dispose of PLX3397, and how to clean products that may be contaminated with PLX3397.

For more information about risks and side effects, ask your study doctor.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

Taking part in this study may or may not make your health better. While doctors hope PLX3397 and eribulin will be more useful against cancer compared to the usual treatment, there is no proof of this. We do know that the information from this study will help doctors learn more about PLX3397 and eribulin as a treatment for cancer. This information could help future cancer patients.

WHAT OTHER CHOICES DO I HAVE IF I DO NOT TAKE PART IN THIS STUDY?

If you choose not to participate in this research study, other procedures or treatments for your cancer could include:

- Getting treatment or care for your cancer without being in a study. Eribulin is a standard option for treatment of metastatic breast cancer available without being in a study. Your doctor can discuss other chemotherapy options with you.

- Taking part in another study.
- Getting no treatment.
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Please talk to your doctor about your choices before deciding if you will take part in this study.

WILL MY MEDICAL INFORMATION BE KEPT PRIVATE?

We will do our best to make sure that the personal information in your medical record is kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- Plexxikon Inc. and Eisai, Inc., and their authorized representatives.
- Government agencies such as the National Cancer Institute (NCI) and the Food and Drug Administration (FDA), involved in keeping research safe for people.
- UCSF's Committee on Human Research
- UCSF Helen Diller Family Comprehensive Cancer Center
- University of California

Participation in research may involve a loss of privacy, but information about you will be handled as confidentially as possible. A medical record will be created because of your participation in this study. Your consent form and some of your research test results will be included in this record. Therefore, your other doctors may become aware of your participation. Hospital regulations require that all health care providers treat information in medical records confidentially.

WHAT ARE THE COSTS OF TAKING PART IN THIS STUDY?

You and/or your health plan/insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for taking part in studies. Check with your health plan/insurance company to find out what they will pay for. Taking part in this study may or may not cost you or your insurance company more than the cost of getting regular cancer treatment.

Plexxikon Inc., the makers of PLX3397, is supplying the study drug free of charge. You will not be billed for any clinic visits or any of the tests required specifically by the study. These are procedures noted above as "study test" (such as tumor biopsies, blood draws for PK, CSF1, and

white blood cell blood tests) in this consent form. Other procedures, which are also done in this study but are part of your normal care, will be paid for by you or your insurance.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

WILL I BE PAID FOR TAKING PART IN THIS STUDY?

You will not be paid for taking part in this study.

WHAT HAPPENS IF I AM INJURED BECAUSE I TOOK PART IN THIS STUDY?

It is important that you tell your study doctor, Hope Rugo, M.D., if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call her at 415-353-7070.

Treatment and Compensation for Injury: If you are injured as a result of being in this study, treatment will be available. The costs of the treatment may be billed to you or your insurer just like any other medical costs, or covered by the University of California, depending on a number of factors. The University does not normally provide any other form of compensation for injury. For further information about this, you may call the office of the Committee on Human Research at 415-476-1814.

WHAT ARE MY RIGHTS IF I TAKE PART IN THIS STUDY?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

WHO CAN ANSWER MY QUESTIONS ABOUT THE STUDY?

You can talk to your study doctor about any questions, concerns, or complaints you have about this study. Contact your study doctor Hope Rugo, M.D., at 415-353-7070.

If you wish to ask questions about the study or your rights as a research participant to someone other than the researchers or if you wish to voice any problems or concerns you may have about the study, please call the Office of the Committee on Human Research at 415-476-1814.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

CONSENT

You have been given copies of this consent form and the Experimental Subject's Bill of Rights to keep.

You will be asked to sign a separate form authorizing access, use, creation, or disclosure of health information about you.

PARTICIPATION IN RESEARCH IS VOLUNTARY. You have the right to decline to participate or to withdraw at any point in this study without penalty or loss of benefits to which you are otherwise entitled.

If you wish to participate in this study, you should sign below.

Date	Participant's Signature for Consent
Date	Signature of the Person Obtaining Consent
Date	Signature of the witness (required if participant is a non-English speaker)

Medications and Foods to Avoid

CC#12751: A Phase Ib/II study of PLX 3397 and Eribulin in Patients with Metastatic Breast Cancer

The following is a list of medications to avoid while you are on this study. If you go to any medical visit, please take this list with you for the doctor's reference. This list is not all-inclusive.

Before you begin treatment, Dr. Rugo or one of her associates will review all medications you are taking. Make sure you talk with Dr. Rugo before you start or stop taking any medications, whenever possible. This information will be reviewed at each study visit.

In addition to the listed medications you should also avoid eating or drinking juice from Seville (sour) oranges, grapefruit, pomegranate, and starfruit.

Generic Name	Brand Names ®	Generic Name	Brand Names ®
Amiodarone	Cordarone	Mesoridazine	Serentil
Amprenavir	Agenerase	Methadone	Methadose, Dolophine
Atazanavir	Reyataz	Moxifloxacin	Avelox
Carbamazepine	Carbatrol, Tegretol	Nafcillin	
Chloramphenicol	Chloromycetin	Nefazodone	Serzone
Chloroquine	Aralen	Nelfinavir	Viracept
Chlorpromazine	Thorazine	Nevirapine	Viramune
Ciprofloxacin	Ciloxan, Cipro, Neofloxin	Nicardipine	Cardene
Cisapride	Propulsid	Oxcarbazepine	Trileptal
Citalopram	Celexa	Pentamidine	Pentam, Nebupent
Clarithromycin	Biaxin	Pentobarbital	Nembutal
Conivaptan	Vaprisol	Phenobarbital	Luminal
Delavirdine	Rescriptor	Phenytoin	Dilantin
Dexamethasone*	Decadron	Pimozide	Orap
Disopyramide	Norpace	Posaconazole	Noxafil
Dofetilide	Tikosyn	Primidone	Mysoline
Droperidol	Inapsine	Procainamide	Pronestyl
Efavirenz	Sustiva	Quinidine	Cardioquin
Erythromycin	Erythrocin	Rifabutin	Mycobutin
Etravirine	Intelence	Rifampin	Rifadin
Flecainide	Tambocor	Rifapentine	Priftin
Fluconazole	Diflucan	Ritonavir	Norvir
Fosamprenavir	Lexiva	Sotalol	Betapace
Fosphenytoin	Cerebyx	St John's Wort	n/a
Gingko Biloba	n/a	Telithromycin	Ketek
Ginseng	n/a	Thioridazine	Mellaril
Haloperidol	Haldol	Vandetanib	Caprelsa
Ibutilide	Corvert	Voriconazole	VFend
Indinavir	Crixivan		
Itraconazole	Sporanox		
Ketoconazole	Oral forms only		
Lopinavir	(+ ritonavir =) Kaletra		

*Short courses (up to weeks and premedication) is ok.

Schedule of Assessments: Phase 1b

Table 8-1 Study Calendar: Phase Ib

Cycle (1 cycle = 21 days)	Comment	Screening		Cycle 1			Cycle 2		Cycle 3 & Beyond		EOT
Real life time clock		**≤4 wks**	**≤2 wks**	**D 1**	**D 2**	**D 8**	**D 1**	**D 8**	**D 1**	**D 8**	**≤ 30 days**
Informed Consent		X									
Registration			X								
History & Exam			X	X		X	X		X		X
ECOG			X	X		X	X		X		
ConMed Review			X	X		X	X	X	X	X	X
Peripheral Neuropathy		X		X			X		X		
CBC w/ 5 part diff.			X	X		X	X	X	X	X	X
Chemistry Panel	BUN, CO2, Cl, K, Na, Creatinine, Glucose (non-fasting), & Magnesium		X	X			X		X		X
Liver Function Tests	ALT, AST, AlkPhos, Total Bilirubin, & Albumin										X
PT/PTT	Completed prior to tumor biopsy		X								
Urine Pregnancy Test	Within 7 days of beginning treatment		X						X		
EKG		X					X				
Eribulin Therapy, IV	Day 1 & 8, q 21 days			X		X	X	X	X	X	
PLX3397 Therapy	Oral			Beginning Cycle 1, Day 1: Daily (self-administered)							
Bone Scan & other imaging	Baseline, then as indicated	X									
CT (C/A/P)	Every 6 weeks	X							X		X
PK Draws				X	X		X				
Blood for CSF1				X	X		X				
Blood for Leukocyte Subtyping				X							
Tumor biopsy	Required for patients w/ accessible tumor		X								
Archived Tumor Tissue	Requested of all participants		X								

**Patients on the modified eribulin dosing schedule will have cycles 28 days long. Day 8 clinic visits will be performed on Day 15 of each cycle.*

Schedule of Assessments: Phase 2

Cycle (1 cycle = 21 days)	Comment	Screening		Lead-In Phase	Cycle 1			Cycle 2			Cycle 3 & Beyond			EOT
Real life time clock		**≤4 wks**	**≤2 wks**	**Day -7 to -6**	**D 1[1]**	**D 8**	**D15**	**D 1[1]**	**D 8**	**D15**	**D 1[1]**	**D 8**	**D15**	**≤ 30 days [7]**
Informed Consent		X												
Registration			X											
History & Exam			X		X	X		X			X			X
ECOG			X		X	X		X			X			
ConMed Review			X		X	X		X	X		X	X		X
Peripheral Neuropathy		X			X			X			X			
CBC w/ 5 part diff.			X		X	X		X	X		X	X		X
Chemistry Panel	BUN, CO2, Cl, K, Na, Creatinine, Glucose (non-fasting), & Magnesium		X		X			X			X			X
Liver Function Tests	ALT, AST, AlkPhos, Total Bilirubin, & Albumin		X		X	X	X	X	X	X	X	X	X	
PT/PTT	Completed prior to tumor biopsy		X											
Urine Pregnancy Test [2]	Within 7 days of beginning treatment		X								X			
EKG [3]		X						X						
Eribulin Therapy, IV[4]	Day 1 & 8, q 21 days				X	X[5]		X	X		X	X		
PLX3397 Therapy	Oral			Beginning With Lead-In Phase (Day -7 to -6): Daily (self-administered)										
Bone Scan & other imaging	Baseline, then as indicated	X												
CT (C/A/P)	Every 6 weeks[9]	X									X			X
Blood for CSF1[6]				X	X			X			X[8]			
Blood for Leukocyte Subtyping[6]				X	X			X			X[8]			
Tumor biopsy	Required for patients w/ accessible tumor		X		X (Day 0/ -1)									
Archived Tumor Tissue	Requested of all participants		X											

**Patients on the modified eribulin dosing schedule will have cycles 28 days long. Day 8 clinic visits will be performed on Day 15 of each cycle.*